

undersigned will be calling to try to arrange a convenient time for the Examiner to conduct it within the next week.

Although no claim amendments are being made, attached is a claim listing for the convenience of the Examiner in reviewing the claims.

REMARKS

The Examiner has rejected claims 129-151, 160-166, and 168-174 under Section 102(b) as anticipated by Boyce et al. In order to anticipate, each and every element set forth in the claim must be disclosed in a single reference. See MPEP Section 2131. Boyce et al. describe, at column 2, an exemplary combinatorial synthesis, in which members from a group of 10 amino acids are selected to form a set of dipeptides ("AA₁ and AA₂") which are coupled to site V₁ on a compound attached to a bead, producing:

10² variants ...[which were] *encoded with eight molecular tags using the binary tagging method described previously....* Finally, the encoded split synthesis procedure above was again employed with eight more tags to complete V₂ by adding AA₃, AA₄ and A_c." [emphasis added]

Boyce et al. go on to describe that following synthesis, as above, of the encoded library:

[A] binding screen was conducted as a solid phase assay in which a sample of the initially colorless bead bound receptor library (1) was treated with a dilute solution of substrate tethered to an intensely colored dye. Binding was detected by simple inspection: receptor library beads which bound to substrate picked up the colored dyes. [col. 2]

The encoded library was then screened for binding with red Leu enkephalin. It was noted that only about 1% of the beads turned bright red, which indicated

significant binding to this labeled enkephalin compound. Proceeding on, the authors state:

We *picked* [about] 50 of these bright red beads and *decoded their synthetic histories by gas chromatography* to identify AA₁ - AA₄ for those receptors which selectively bound [red Leu enkephalin]. [emphasis added]

Boyce et al. do not disclose any of the following three elements (designated as (i), (ii) and (iii) in the claim 1 set forth below) of claim 129:

decoding the code composed of one or more tag(s) to identify the compound associated with the code, wherein the decoding step is carried out [i] without isolating the solid support of interest from other solid supports and [ii] without detaching any of the tags from the solid support of interest and wherein [iii] the decoding step comprises in-situ optical interrogation of the tag(s).

In Boyce et al. the solid support of interest *is isolated* from other solid supports ("We then picked [about] 50 of these bright red beads ..."); the tags *are detached* from the solid support ("[We] decoded their synthetic histories by gas chromatography ...") as gas chromatography necessitates volatilizing the tags, thereby "detaching" them from the solid support¹; and, because gas

¹Moreover, the gas chromatography analysis of the tags mentioned here would likely involve first chemical removal ("detachment") of the tags, followed by gas chromatography analysis. This is made clear in Still et al., US Patent No. 5,565,324, cited and relied on herein by the Examiner (note that Still is the corresponding author of the Boyce et al. reference; thus, the Boyce et al. group was likely following the same method as in this patent). At col. 49, lines 47-56, Still et al. state:

A single, selected bead was placed in a Pyrex capillary tube and washed with DMF The bead was then suspended in DMF ... and the capillary was sealed. The suspended bead was irradiated at 366 nm for 3 hrs *to release the tag alcohols*, and the capillary tube subsequently placed in a sand bath at 90 DEG C for 2 hrs. The tube was opened and bis-trimethylsilyl acetamide (0.1 mL) was added to trimethylsilylate the tag alcohols. After centrifuging for 2 min., *the tag solution above the bead ... was injected directly into an electron capture detection, capillary gas chromatograph* for analysis. [emphasis added]

chromatography is the method for decoding, the decoding step *does not include* "in-situ optical interrogation of the tag(s)."

At page 4, second from last sentence, the Examiner states:

[Boyce et al.] discloses that many beads had developed light orange coloration and few turned bright red (refers to said decoding step comprises in-situ optical interrogation of the instant claims). The reference discloses that bright red beads (refers to other solid supports) and decoded their synthetic history.

But the red and light orange color of the beads was not used for decoding the synthetic histories of the receptors in the library (and could not be so used, as these two colors alone could not encode the 10^4 different receptor compounds in the library). That some beads turned red or light orange indicated only that certain receptor compounds in the Boyce et al. library had a "property of interest" (see step (f) of claim 1), *i.e.*, the assay indicated that such receptor compounds bound to red Leu enkephalin. The rejection should be withdrawn.

The Examiner has also upheld the rejection of claims 129-138, 142-146, 151, 154 and 159 under Section 102(b) as anticipated by Dower et al. The Examiner has noted on page 7, lines 8-10, that independent claim 129 recites: "... decoding the code composed of the tag to identify the compound associated with the code, ...wherein the decoding step comprises in-situ optical interrogation of the tag." On the same page 7, lines 1 to 3, the Examiner states that: "the features on which applicant relies (*i.e.*, determining the sequence or structure of the compound attached to the bead by in-situ optical interrogation) are not recited in the rejected claim(s)." Given that claim 129 recites that the tag is decoded by in-situ optical interrogation to *identify the compound*, the "sequence

or structure" of the compound is also necessarily determined by the recited in-situ optical interrogation. The identity of a compound *is* its "sequence or structure"; they are one and the same thing. One cannot "identify" a compound without either naming it (which identifies its sequence or structure) or drawing it (which identifies its sequence or structure).

Moreover, as noted in the prior response, Dower et al. do not disclose decoding of beads which are tagged, no matter how they are labeled, *without* isolation of the beads to be decoded. Beads to be decoded are always isolated. See, Dower *et al.*, *e.g.*, at page 30, lines 5-25. In contrast, in claim 129: "the decoding step is carried out without isolating the solid support of interest from other solid supports..." This is clearly not disclosed in Dower et al., and therefore, the rejection under Section 102(b) should be withdrawn.

The Examiner also states on page 7 that: "Dower et al. teach after the receptor assay the positive beads are identified by visual inspection of the fluorescent beads ..." In a preferred embodiment of Dower et al., the identifier tag is an oligonucleotide, which is necessarily decoded by sequencing, not by in-situ optical interrogation. See Dower et al., page 4, lines 21 to 33. In another preferred embodiment of Dower et al.: "the identifier tag may be a set of light-addressable compounds, such as fluorescent or phosphorescent compounds that can be photobleached, which compounds are incorporated into the beads or particles on which the oligomers of the oligomer library are synthesized. ..." See Summary of the Invention, page 4, line 34 to page 5, line 2. But this embodiment is not elaborated on, and specific methods for decoding of these tags are not

described. The decoding methods described in Dower et al. all involve isolation of the beads to be decoded, leading to the conclusion that these light-addressable tags are also to be decoded in this same manner, rather than "without isolating the solid support of interest from other solid supports..." as required in claim 129. Accordingly, this claim is not anticipated.

The Examiner has rejected claims 129-138, 142-146, 151, and 155-159 under Section 102(b) as anticipated by Still et al. The Examiner states, with respect to Still et al., that:

The reference discloses that the beads with ligand attached are incubated in an aqueous buffer with monoclonal antibody (for the property to be tested), and the fluorescent beads with attached monoclonal antibody are identified and separated by manually or using FACS from the unstained beads, so long as the tags are retained on the bead under the conditions of sorting. The reference teaches that the fluorescent beads with attached compound are identified from the unstained beads, thus, the reference analyzed the fluorescent data of the beads, to identify the compound of interest in the library. Thus, the reference clearly anticipates the claimed invention. [page 8, end of first paragraph]

Because the fluorescent beads with the attached monoclonal antibodies are identified and separated from the unstained beads manually or by FACS *before* identification of the compound of interest, it is clear that the decoding step is *not* "carried out without isolating the solid support of interest from other solid supports," as required in claim 129.

The Examiner also states (pages 8-9) that Applicants arguments regarding patentability over Still et al. "are not persuasive," because:

Still et al. teach that families of compounds can be employed as identifiers, where the number and/or position of a substituent define the choice, and alternatively detectable functionalities such as radioisotopes, fluorescers, halogens can be used. And the reference after synthesis is

completed, the reaction products are screened for desired property by incubating the beads with fluorescently labeled Antibody and the positive beads are identified and separated, which refers to the in-situ optical interrogation of the beads to identify the compound with desired biological property of the instant claims.

In contrast to the Examiner's assertion, the portions of Still et al. referring to "incubating beads with fluorescently labeled antibody" are not referencing "in-situ optical interrogation of the beads to identify the compound ..." Rather, where Still et al. refer to incubating of beads with fluorescently labeled antibody, they are referring to screening of the beads for a "property of interest," as in the assay in step (f) of claim 129. For example, col. 29, lines 65 to col. 30, line 29, discuss that to "determine the characteristic of interest of the product ... one may provide for an antibody to the receptor, where the antibody is labeled...."

In contrast to these portions of Still et al. referring to labeled antibodies, at col. 28, lines 59-65, fluorescent tags for compound identification are discussed:

While fluorescent tags alone may not be sufficient to define a significant number of stages with a significant number of choices ... by providing means for separating the fluorescent tagging molecules based on variations in C or C' one can individually detect the tags by their fluorescence.

It is again clear that the decoding step of such fluorescent tagging molecules is *not* "carried out without isolating the solid support of interest from other solid supports," as required in claim 129.

The Examiner also states on page 9 that:

Applicants' arguments seem to be emphasizing that applicants decoding refers to identifying the structure of the compound, not identifying the positive compound attached to the bead from among other beads.... It is noted that the features upon which applicant relies (i.e., decoding the code

to determine the structure of the compound) are not recited in the rejected claim(s).

Exactly where Applicants' prior arguments refers to "identifying the structure of the compound" or "decoding the code to determine the structure of the compound" is not understood. Nevertheless, as noted above, in claim 129, where the tag is decoded by in-situ optical interrogation to *identify the compound*, Applicants do agree that the "sequence or structure" of the compound is also necessarily determined by the recited in-situ optical interrogation. The identity of a compound *and* its "sequence or structure" are one and the same thing.

The Examiner also states that:

Still et al. teach after the synthesis is completed, the compounds are screened for desired property either after detachment of the ligand (compound) from the bead or while still attached, which clearly anticipates the claimed invention.

The fact that the assay for the "desired property" can be carried out while the ligand/compound is still attached to the beads, does not change the fact that Still et al. state that the "identifiers contain a cleavable member or moiety which permits detachment of a component which can be readily analyzed." See Col. 3, lines 36-38; Summary of the Invention. There are no statements in Still et al. that the tag/identifier does not get removed from the bead for decoding; they consistently state that it in fact *does* get removed. See, e.g., col. 17, lines 16-18 ("Each selected fluorescent bead is subjected to a means for releasing at least some of the tags from the bead.") Thus, for this reason alone, claim 129, which

requires decoding "without detaching any of the tags from the solid support of interest," is not anticipated.

The Examiner has also maintained the rejection of claims 129-159 under Section 103(a) (and added such rejection of claims 160-166 and 168-174) over Dower et al. in view of Metzeker et al. The Examiner supports the rejection alleging that the "claimed invention differs from the prior art teachings by reciting that the fluorescent tags of specific chemical structures." This is not correct, because there are additional significant differences between the cited art and the claimed invention. As noted above, Dower et al. fail to disclose that "the decoding step is carried out without isolating the solid support of interest from other solid supports..." as required in claim 129. Dower et al. in fact teach away from this step. In the principal preferred embodiment of Dower et al., the identifier tag is an oligonucleotide, which is decoded by sequencing, which necessarily requires isolation of the tagged solid support prior to sequencing. Therefore, Dower et al. would motivate one *not* to carry out "the decoding step ... without isolating the solid support of interest from other solid supports..." as required in claim 129.

Another preferred embodiment is mentioned in the Summary of the Invention section of Dower et al.², but there is no suggestion that the identifiers referred to there can be decoded without isolation of the solid supports carrying them, and, in view of the repeated statements in Dower et al. that decoding of

² As noted above, in this embodiment: "the identifier tag may be a set of light-addressable compounds, such as fluorescent or phosphorescent compounds that can be photobleached, which compounds are incorporated into the beads or particles on which the oligomers of the oligomer library are synthesized. ..."

identifiers is performed following isolation of the solid supports, there clearly is a teaching away from that required step in claim 129. Metzeker does not disclose either of these required steps either. Accordingly, combining these references in any manner would not suggest the claimed invention or motivate one to make it.

The Examiner has also used, in support of the conclusion of obviousness, a quote from Section 2145 IV. of the MPEP, that: "One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This statement does not imply, however, that it is in any way incorrect to note that there is no suggestion or motivation to combine the prior art as would be required to achieve the invention. See, e.g., MPEP 2143.01, para. 3 ("Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.") Noting the lack of suggestion or motivation to combine the prior art, and/or noting teachings away, is the manner in which nonobviousness is established in all cases, following a rejection.

Accordingly, the rejection under Section 103(a) should also be withdrawn, and as all claims are dependent on claim 129, and it is clearly allowable, a notice of allowance is earnestly requested.

Respectfully submitted,

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Claim Listing

1. -128. (canceled).

129. (previously presented) A method of identifying a compound of interest in a library of compounds, each of said compounds being bound to a solid support and being produced by a unique reaction series composed of N reaction steps, wherein N is an integer of at least 2, and wherein each compound is produced from components which are independently the same or different, the method comprising:

- (a) dividing a population of solid support into M batches, wherein M is an integer greater than 1;
- (b) reacting each of the M batches of solid support with a component, so that the component forms a bond with the solid support;
- (c) adding to one or more batches, prior to (b), concurrently with (b), or subsequently to (b), one or more tag(s), each tag able to be attached to the solid support and able to be identified by optical interrogation, wherein said one or more tag(s) constitutes a code, which code is uniquely associated with a compound and a corresponding reaction sequence and is determined by optical interrogation;
- (d) recombining all of said M batches after (b) and (c);
- (e) repeating (a) to (d) for N-1 times, or repeating (a) to (d) for N-2 times followed by repeating (a) to (c) once, to produce a library of compounds;

(f) performing an assay capable of indicating that any compound in the library has a property of interest; and

(g) decoding the code composed of one or more tag(s) to identify the compound associated with the code, wherein the decoding step is carried out without isolating the solid support comprising the compound having the property of interest from other solid supports and without detaching any of the tags(s) from the solid support comprising the compound having the property of interest, and wherein said decoding step comprises in-situ optical interrogation of the tag(s).

130. (previously presented) The method of claim 160 wherein the solid support comprises a bead.

131. (previously presented) The method of claim 160 wherein (c) comprises repeating (a) to (d) for N-1 times to produce a library of compounds.

132. (previously presented) The method of claim 160, wherein (e) comprises repeating (a) to (d) N-2 times followed by repeating (a) to (c) once to produce a library of compounds.

133. (previously presented) The method of claim 132, further recombining said M batches subsequent to contacting the library of compounds with the target biomolecule

134. (previously presented) The method of claim 160, wherein each fluorophore tag is in substoichiometric amount compared to the component added in (b).

135. (previously presented) The method of claim 160, wherein each fluorophore tag added in (c) is from about 0.001 to about 0.1 molar equivalent to the component added in (b).

136. (previously presented) The method of claim 160, wherein the optical interrogation of each fluorophore tag comprises determining its relative abundance.

137. (previously presented) The method of claims 160, wherein each fluorophore tag is attached to the solid support by covalent bonding.

138. (previously presented) The method of claim 160, wherein the fluorophore tag is capable of forming a bond to the solid support directly or to the component attached to said solid support.

139. (previously presented) The method of claim 160, wherein the fluorophore tag is a dye selected from the group consisting of compounds with the following chemical structures:

3-(ϵ -carboxypentyl)-3'-ethyl-oxacarbocyanine-6,6'-disulfonic acid,

1-(ϵ -carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid,

1-(ϵ -carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indocarbocyanine-5,5',7,7'-tetrasulfonic acid, and

1-(ϵ -carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid,

and is activated as an active ester selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

140. (previously presented) The method of claim 160, wherein the fluorophore tag is a dye selected from the group consisting of compounds with the following chemical structures:

6-((4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino) hexanoic acid,

6-((4,4-difluoro-5-phenyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino) hexanoic acid,

6-((4,4-difluoro-1,3-dimethyl-5-(4-methoxyphenyl)-4-bora-3a,4a-diaza-s-indacene-2-propionyl) amino)hexanoic acid,

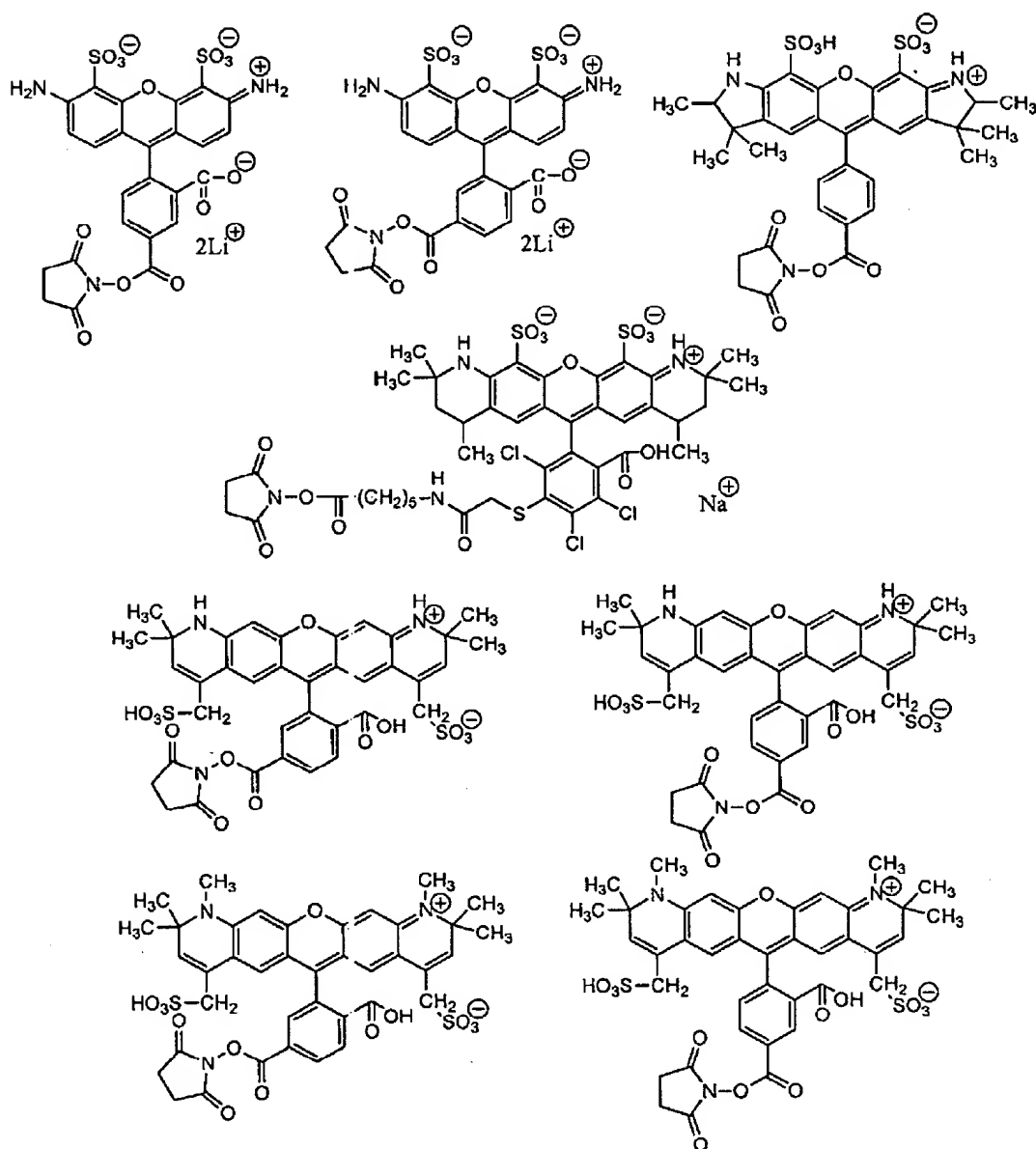
6-(((4-(4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl)phenoxy) acetyl) amino)hexanoic acid,

6-(((4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl)styryloxy)acetyl) aminohexanoic acid, and

6-(((4,4-difluoro-5-(2-pyrrolyl)-4-bora-3a,4a-diaza-s-indacene-3-yl)styryloxy) acetyl)aminohexanoic acid,

and is activated as an active ester selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

141. (previously presented) The method of claim 160, wherein the fluorophore tag is a dye selected from the group consisting of compounds with the following chemical structures:



142. (previously presented) The method of claim 160, wherein (g) is carried out using multi-color fluorescence imaging or spectral imaging analysis.

143. (previously presented) The method of claim 160, wherein the decoding is carried using multi-color fluorescence imaging in combination with spectral analysis.

144. (previously presented) The method of claim 160, wherein M is an integer from at least 2 to 25.

145. (previously presented) The method of claim 160, wherein the component is protected or unprotected at a group which is capable of participating in a further coupling reaction and orthogonally protected at non-participating group(s), and wherein (d) further comprises cleaving any protecting group of the component which is to participate in a further coupling reaction.

146. (previously presented) The method of claim 160, wherein the fluorophore tag is optically distinguishable by emission wavelength.

147. (previously presented) The method of claim 160, wherein the fluorophore tag is optically distinguishable by emission intensity by adjusting the ratio of the relative quantities of the fluorophore tags.

148. (previously presented) The method of claim 147, wherein the ratio is from about 1:1 to 4:1.

149. (previously presented) The method of claim 160, wherein the fluorophore tag is optically distinguishable by excited-state lifetime.

150. (previously presented) The method of claim 160, wherein the fluorophore tag is optically distinguishable by emission wavelength, excited-state lifetime and emission intensity.

151. (previously presented) The method of claim 160, wherein the compound of interest comprises an oligonucleotide or nucleic acid.

152. (withdrawn) The method of claim 129, wherein the compound of interest comprises an oligopeptide or a protein.

153. (withdrawn) The method of claim 129, wherein the compound of interest comprises a ligand.

154. (previously presented) The method of claim 160, wherein N is an integer from at least 4 to about 12.

155. (previously presented) The method of claim 130, wherein the decoding is carried out while the beads are on a planar substrate.

156. (previously presented) The method of claim 155 wherein the optical interrogation is carried out using multi-color fluorescent imaging in combination with spectral analysis.

157. (previously presented) The method of claim 130, wherein the decoding is carried out while the beads are arranged in a planar bead array.

158. (previously presented) The method of claim 157 wherein the optical interrogation is carried out using multi-color fluorescent imaging in combination with spectral analysis

159. (previously presented) The method of claim 130, wherein the bead is composed of a material selected from the group consisting of polystyrene, polyethylene, cellulose, polyacrylate, polyacrylamide, silica and glass.

160. (previously presented) The method of claim 129, wherein the tag in (c) comprises a fluorophore tag.

161. (previously presented) The method of claim 129 wherein the tag in (c) comprises a chromophore tag.

162. (previously presented) The method of claim 129 wherein the code is a binary code, an extended binary code, or a simple code.

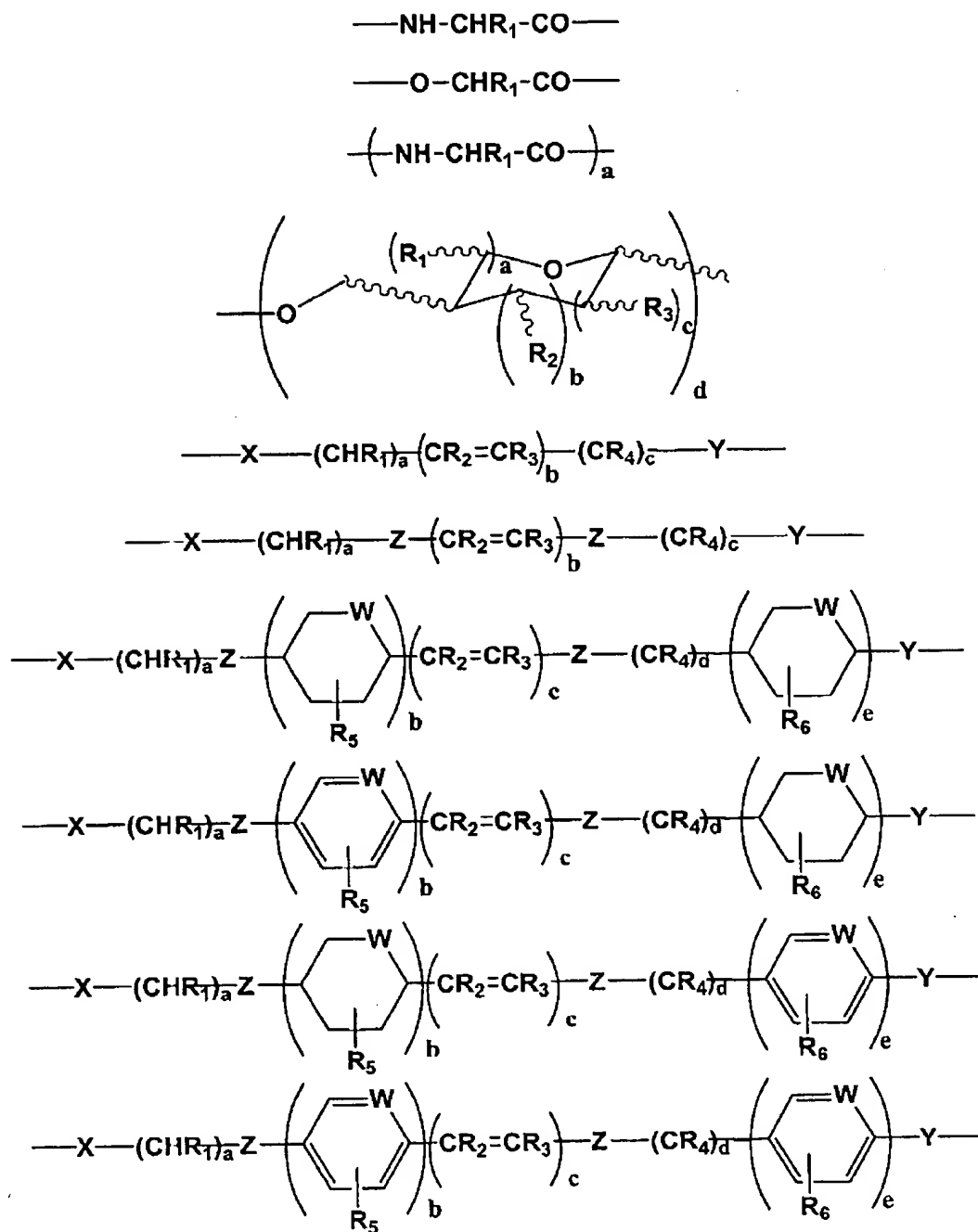
163. (previously presented) The method of claim 147, wherein a difference in emission intensity is the result of a difference in the ratio of relative quantities of fluorophore tags.

164. (previously presented) The method of claim 129, wherein the property of interest is a binding affinity of a compound to a receptor, the assay is performed by determining a physical response to binding by:

- (a) first admixing with the library of compounds a solution of a labeled receptor so as to result in labeled receptor bound to at least one compound bound to a solid support;
- (b) removing the solution from the solid support;
- (c) optionally washing the solid support so as to substantially remove non-bound labeled receptor; and
- (d) measuring the physical response due to bound labeled receptor so as to determine the binding affinity.

165. (previously presented) The method of claim 164, wherein the receptor is labeled by a fluorescent dye, a colored dye, a radioisotope or an enzyme.

166. (previously presented) The method of claim 164, wherein the physical response is fluorescence emission, optical absorption or radioactivity.
167. (withdrawn) The method of claim 129, wherein the components have a structure independently selected from the group consisting of:



wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are independently methyl, ethyl, linear or branched chain C_3 - C_9 , phenyl, benzoyl, cyano, nitro, halo, formyl,

acetyl and linear or branched chain C₃-C₉ acyl; wherein a, b, c, d and e are independently 0, 1, 2 or 3; wherein X, Y and Z are independently NH, O, S, S(=O), CO, (CO)O, O(CO), NH(C=O) or (C=O)NH; and wherein W is independently N, O or S.

168. (previously presented) The method of claim 129, wherein the assay is performed by cleaving compounds from the solid support while permitting diffusion through solution and binding to receptors, said receptors arranged in proximity to each solid support.

169. (previously presented) The method of claim 129, wherein the decoding step comprises the steps of:

- (a) collecting spectral fluorescence data for each respective solid support so as to determine the respective abundance of the tag(s) bound thereto; and
- (b) analyzing the collected spectral fluorescence data by comparing the respective relative abundances of the tag(s) determined in (a) so as to determine the unique reaction series for the component, thereby identifying the compound having the property of interest.

170. (previously presented) The method of claim 169 wherein the solid support is a bead.

171. (previously presented) The method of claim 170 wherein spectral fluorescence data is collected by:
- (a) forming a static planar array or a dynamic planar array of beads; and
 - (b) obtaining a fluorescence image for each bead.
172. (previously presented) The method of claim 171, wherein the planar array of beads is formed adjacent to the planar walls of a sandwich flow cell and controlled by light-controlled electrokinetic means.
173. (previously presented) The method of claim 170, wherein spectral fluorescence data are collected for the bead array by initially forming a spatially encoded array of beads at an interface between an electrode and an electrolyte solution, comprising the following steps:
- (a) providing an electrode and an electrolyte solution;
 - (b) providing multiple types of beads, each type being stored in accordance with chemically or physically distinguishable bead characteristics in one of a plurality of reservoirs, each reservoir containing a plurality of like-type beads suspended in said electrolyte solution;

- (c) providing said reservoirs in the form of an *mxn* grid arrangement;
- (d) patterning said electrode to define *mxn* compartments corresponding to said *mxn* grid of reservoirs;
- (e) depositing *mxn* droplets from said *mxn* reservoirs onto said corresponding *mxn* compartments, each said droplet originating from one of said reservoirs and remaining confined to one of said *mxn* compartments and each said droplet containing at least one bead;
- (f) positioning a top electrode above said droplets so as to simultaneously contact each said droplet;
- (g) generating an electric field between said top electrode and said *mxn* droplets;
- (h) using said electric field to form a bead array in each said *mxn* compartments, each said bead array remaining spatially confined to one of said *mxn* droplets;
- (i) illuminating said *mxn* compartments on said patterned electrode with a predetermined light pattern to maintain the position of said bead arrays in accordance with said predetermined light pattern and the pattern of *mxn* compartments; and
- (j) positioning said top electrode closer to said electrode thereby fusing said *mxn* droplets into a continuous liquid

phase, while maintaining each of said *mxn* bead arrays in one of the corresponding *mxn* compartments.

174. (previously presented) The method of claim 173, wherein said compartments are hydrophilic and the remainder of said electrode surface is hydrophobic.